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Pharmacological investigation of mono-, di- and tri-organotin(IV) derivatives of carbodithioates: Design, spectroscopic characterization, interaction with SS-DNA and POM analyses

Muhammad Sirajuddin [a,b,*], Saqib Ali [b,*], Muhammad Nawaz Tahir [c]

[a] Department of Chemistry, University of Science & Technology, Bannu, Pakistan
[b] Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan
[c] Department of Physics, University of Sargodha, Sargodha, Pakistan

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ABSTRACT

Ten complexes of sodium salt of pyrrolidine-1-carbodithioate with mono, di and tri-organotin(IV) derivatives, [$SnR_3(S_2CR')$; {R′ = pyrrolidine, R = CH_3 (**1**), C_2H_5 (**2**) C_6H_{11} (**3**), CH_2-C_6H_5 (**4**)}; $SnR_2(S_2CR')_2$; {R = CH_3 (**5**), $C(CH_3)_3$ (**6**) CH_2-C_6H_5 (**7**)}; $SnRCl_2(S_2CR')$; {R = C_4H_8 (**8**), C_6H_5 (**9**, **10**)}], have been synthesized and characterized by elemental, FT-IR and multinuclear NMR (^1H, ^{13}C and ^{119}Sn) techniques. The FT-IR data reveals that in triorganotin(IV) the CSS unit acts as a monodentate ($\Delta\nu_{asym}$ is >20) while in mono and diorganotin(IV) derivatives it acts bidentate as the difference (a single and unsplit peak is observed). The crystal structures of the complexes **3**, **5**, **6** and **9** were also determined by X-ray single crystal analysis. In complex **3** the geometry around of tin atoms is 4-coordinated tetrahedral while complex **9** demonstrated 5-coordinated geometry trigonal bipyramidal. Complexes **5** and **6** show 6-coordinated octahedral geometry. They were also screened for interaction with DNA by UV–visible spectroscopy. From the UV–visible spectroscopic result it was confirmed that the binding mode of these compounds with DNA is an intercalation. This was further conformed by viscosity measurements. The screening results show that the complex exhibit good antibacterial activity. POM analyses reveal that the compounds are slightly toxic and present a potential antibacterial activity. Moreover, they have 5–85% drug score which is an important parameter for the compound possessing the drug properties.

1. Introduction

Due to extensive applications of organotin compounds, their synthesis and characterization with variety of O-, S- and N-containing ligands have been a continuing subject in recent years [1]. In addition to synthesis and structural elucidation organotin compounds are extensively studied for their biological activities. Among the variety of the ligands, organotin complexes of dithiocarbamates have been extensively studied because of their variety of structures and biological activities [2–5]. The organotin derivatives of dithiocarbamates are also subjected to thermal and CVD studies [1].

Now a day much concentration have been paid to the synthesis, characterization and biological activities of various organotin(IV) derivatives with sulfur ligands like dithiocarbamate [6,3]. Universal attention in organotin complexes have been geared by their potential therapeutic use as antifungal, antibacterial, and antitumoral agents. Mostly, these compounds are organotin(IV) derivatives with carboxylates, aminoacids, heterocycles and various N, O, or S donor ligands, particularly dithiocarbamates, given that sulfur ligands coordinated to diorganotin moieties were regarded as very stable in comparison to other ligands coordinated by N or O [7,8]. Tin complexes as well as dithiocarbamates ligands are known for their biological interest as antifungal, antibacterial and biocide agents. Therefore, the coordination of tin with dithiocarbamates would enhance such biological aspects [8]. Further interest in the structural features of organotin(IV) dithiocarbamate complexes is based on the wide range of industrial applications such as chemical vapor deposition processes, flame retardants, polymer stabilizers, and non-linear optical materials [9]. The dithiocarbamate moiety has received much attention in recent years due to its ability to act as a bidentate ligand [10–12]. Dithiocarbamates such as diethyldithiocarbamate and pyrrolidinedithiocarbamate display cytotoxic properties and they have been used to fight against metal

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* Corresponding authors at: Department of Chemistry, University of Science & Technology, Bannu, Pakistan (M. Sirajuddin), Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan (S. Ali). Tel.: +92 51 90642130; fax: +92 51 90642241.

E-mail addresses: m.siraj09@yahoo.com (M. Sirajuddin), drsa54@hotmail.com (S. Ali).

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poisoning. Due to their ability to form thermodynamically stable complexes, they are also used as chelating agents for the extraction of trace metals. Metal complexes of dithiocarbamates present a wide range of applications in agriculture, medicines, industry and, in analytical and organic chemistry. The use of dithiocarbamate complexes in the rubber vulcanization process is an example of their commercial importance [13].

Keeping in view the structural and biological diversity of organotin(IV) compounds, here we present the synthesis, characterization, *in vitro* biological activity and interaction with SS-DNA as well as POM analyses of pyrrolidine-1-carbodithioate based organotin(IV) complexes.

2. Experimental

2.1. Materials and methods

Reagents Me_3SnCl, Et_3SnCl, Cy_3SnCl, Me_2SnCl_2, t-Bu_2SnCl_2, $BuSnCl_3$, $PhSnCl_3$, pyrrolidine and CS_2 were obtained from Aldrich (USA) and were used without further purification. All the solvents purchased from E. Merck (Germany) were dried before use according to literature procedures [14]. Dibenzyltin dichloride (Bz_2SnCl_2) and tribenzyltin chloride (Bz_3SnCl) were prepared according to the reported method [15]. Sodium salt of Salmon fish sperm DNA (SS-DNA) (Arcos) was used as received. The melting points were determined in a capillary tube using a Gallenkamp (UK) electrothermal melting point apparatus. IR spectra in the range of 4000–100 cm^{-1} were obtained on a Thermo Nicolet-6700 FT-IR Spectrophotometer. Elemental analysis was done using a CE-440 Elemental Analyzer (Exeter Analytical, Inc). ^1H, ^{13}C and ^{119}Sn NMR were recorded on a 400 MHz JEOL ECS instrument, using $CDCl_3$ as an internal reference [$^1H(CDCl_3\text{-}d3) = 7.28$ and $^{13}C(CDCl_3\text{-}d3) = 77$ ppm]. Tetramethylsilane (for ^1H and ^{13}C NMR) and Me_4Sn (for ^{119}Sn NMR) were used as external standards. For ^{119}Sn NMR the measurement was recorded at a working frequency of 37.29 MHz and the chemical shift was referenced to Me_4Sn as an external standard. Chemical shifts are given in ppm and coupling constants (J) values are given in Hz. The multiplicities of signals in ^1H NMR are given with chemical shifts; (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The absorption spectra were measured on a Shimadzu 1800 UV–Visible Spectrophotometer. Complexes **3**, **6** and **7** were collected at room temperature on a Bruker Apex II CCD diffractometer. Complex **9** was collected at 190 (2) K on Agilent Super Nova (Dual, Cu at zero, Eos) diffractometer. All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters, and hydrogen atoms bonded to carbon were inserted at calculated positions using a riding model. Hydrogen atoms bonded to O or N were located from difference maps and their coordinates refined. SHELXTL [16] was used to solve and SHELX2012 [17] to refine the structures. Viscosity was measured by Ubbelohde viscometer at room temperature.

2.2. Synthesis

2.2.1. Synthesis of pyrrolidine-1-carbodithioic acid (**HL**) and sodium pyrrolidine-1-carbodithioate (**NaL**)

The ligand (**HL**) was prepared by the reaction of stoichiometric amounts of pyrrolidine and CS_2 in 50 mL of absolute methanol at room temperature. The solution was stirred at room temperature for 4 h and precipitates appeared. The precipitates were filtered, washed with diethyl ether and then air dried. Sodium salt of the ligand (NaL) was prepared by the addition of an aqueous solution of sodium hydrogen carbonate ($NaHCO_3$) to a suspended solution of **HL** in distilled water. The mixture was stirred at room temperature to get a clear solution which was then rotary evaporated to get the desired sodium salt of the ligand. The chemical reaction is shown in Scheme 1.

2.2.2. Procedure for the synthesis organotin(IV) complexes

Stoichiometric amount of sodium salt of pyrrolidine-1-carbodithioate was suspended in dry toluene and to it calculated amount of organotin(IV) chloride, [{for R_3SnCl: NaL = 1:1 molar ratio (for Complexes **1**–**4**)}; {for R_2SnCl_2: NaL = 1:2 molar ratio (for Complexes **5**–**7**)}; {for $RSnCl_3$: NaL = both 1:1 molar ratio (for Complexes **8**–**9**) and 1:2 molar ratio (for Complex **10**)}], was added. The mixture was stirred and refluxed for 3–4 h, and then it was cooled and filtered to remove NaCl. The filtrate was rotary evaporated to get the product which was recrystallized in chloroform. The chemical reaction is shown in Scheme 1.

2.2.3. DNA interaction study assay by UV–visible spectroscopy

SS-DNA (50 mg) was dissolved by overnight stirring in deionized water (pH = 7.0) and kept at 4 °C. Deionized water was used to prepare buffer (20 mM Phosphate buffer (NaH_2PO_4-Na_2HPO_4), pH = 7.2). A solution of (SS-DNA) in the buffer gave a ratio of UV absorbance at 260 and 280 nm (A_{260}/A_{280}) of 1.8, indicating that the DNA was sufficiently free of protein [18–20]. The DNA concentration was determined *via* absorption spectroscopy using the molar absorption coefficient of 6600 M^{-1} cm^{-1} (260 nm) for SS-DNA [21–23] and was found to be 1.8×10^{-4} M. The compound was dissolved in DMSO at a concentration of 1 mM. The UV absorption titrations were performed by keeping the concentration of the compound fixed while varying the SS-DNA concentration. Equivalent solutions of SS-DNA were added to the complex and reference solutions to eliminate the absorbance of DNA itself. Compound-DNA solutions were allowed to incubate for about 10 min at room temperature before measurements were made. Absorption spectra were recorded using cuvettes of 1 cm path length at room temperature (25 ± 1 °C).

2.2.4. Viscosity measurements

Viscosity measurements were carried out using Ubbelohde viscometer at room temperature (25 ± 1 °C). Flow time was measured with a digital stopwatch. Each sample was measured three times and an average flow time was calculated. Data were presented as relative viscosity, $(\eta/\eta_o)^{1/3}$, *vs.* binding ratio ([Compound]/[DNA]) where η is the viscosity of DNA in the presence of complex and η_o is the viscosity of DNA alone. Viscosity values were calculated from the observed flow time of DNA containing solution (η_o), $\eta_o = t - t_o$ [24].

2.2.5. Cytotoxicity

Cytotoxicity was studied by brine-shrimp lethality assay method [25,26]. Brine-shrimp (Artemia salina) eggs were hatched in artificial sea water (3.8 g sea salt/L) at room temperature (22–29 °C). After two days these shrimps were transferred to vials containing 5 mL of artificial sea water (10 shrimps per vial) with 10, 100 and 1000 μg/mL final concentrations of each compound taken from their stock solutions of 12 mg/mL in DMSO. After 24 h number of surviving shrimps was counted. Data were analyzed with a biostat 2009 computer program (Probit analysis) to determine LD_{50} values.

2.2.6. Petra/Osiris/Molinspiration (POM) analyses

Petra/Osiris/Molinspiration analysis (POM) is one of the well-known approach that has been used regularly to produce the two dimensional models to identify and to indicate the type of pharmacophore site that affects biological activity with a change in the chemical substitution. The advantages of POM are the ability to predict the biological activities of the molecules and to represent the relationships between steric/electrostatic property as well as